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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/700,472	11/05/2003	Edward Green	000487.00026	7751

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BANNER & WITCOFF  
1001 G STREET N W  
SUITE 1100  
WASHINGTON, DC 20001

EXAMINER

MEAH, MOHAMMAD Y

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 09/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No. 10/700,472	Applicant(s) GREEN ET AL.	
	Examiner Mohammad Meah	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
  - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
  - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 13 June 2006.
- 2a) ☐ This action is **FINAL**.      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-4, 7-12, 15 and 16 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-4, 7-12, 15 and 16 is/are rejected.
- 7) ☐ Claim(s) 2-4, 7-12, 15 and 16 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All. b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>11/05/03</u>  | 6) <input type="checkbox"/> Other: _____                          |

### **DETAILED ACTION**

Claims 1-20 are pending. In response to the election/restriction-office action of date 06/13/2006 of this application, the applicant, on date 07/05/2006 elected with traverse Group I (claims 1-4, 7-12, 15 and 16) for examination.

### ***Election/Restriction***

During preliminary amendment of this application, the applicant, on date 07/05/2006 elected with traverse Group I (claims 1-4, 7-12, 15 and 16) drawn to gram-positive bacteria having alcohol dehydrogenase (ADH) activity transformed with pyruvate decarboxylase (PDC) gene for examination. Group II (claims 5-6, 13-14 and 17-20) of election/restriction-office action of date 06/03/2006 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected Groups.

Applicants arguments that (1) group II claims (in comparison to group I further comprise lactate dehydrogenase (LDH) gene) comprises species within the genus of group I claims and (2) there would be no undue burden on the examiner to examine all claims directed gram-positive bacteria because of genus-species relationship are found not persuasive because: (1) Group I and II are two distinct groups as explained in election/restriction-office action of date 06/03/2006 that is group II gram-positive bacterium (transformed with pdc gene and having an inactivated ldh gene) has different function, properties and utilities than gram-positive bacterium (transformed with only pdc gene) of group I.

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(2) while the search for each of these distinct groups would be overlapping it would not be coextensive. Art that applies gram-positive bacteria with ADH activity expressed with PDC gene may or may not be relevant to that of gram-positive bacteria with ADH activity expressed with PDC and LDH genes. Therefore the restriction is maintained and made FINAL.

### ***Claim Objections***

Claims 2-4, 7-12, 15 and 16 are objected to because of the recitation "A Gram-positive --", which is refers to a previous claim. "A Gram-positive --" should be changed to "The gram-positive—". Appropriate correction is required.

Claims 9 and 12 are objected in recitation of "adh" and "pdc". Abbreviations unless otherwise obvious and/or commonly used in the art, should not be recited in the claims without at least one reciting the entire phrase for the abbreviation. It is suggested that the term "alcohol dehydrogenase" and "pyruvate decarboxylase" be mentioned for "adh" and "pdc" respectively at least once in prior claim(s)

### ***Claim Rejections***

#### **35 U.S.C 112**

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly

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connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are directed to a genus of gram-positive bacteria having alcohol dehydrogenase activity(adh) transformed with any heterologous pdc gene. The gram positive bacterium transformed with any pdc gene encoding any pyruvate decarboxylase comprise a genus of gram positive bacterium is a large variable genus containing many pdc gene encoding many pyruvate decarboxylase . Therefore, many structurally distinct nucleic acids are encompassed within the scope of these claims. The specification discloses only a few species of the claimed genus (i.e., that of SEQ ID NOs:1-5) which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. A sufficient written description of a genus of DNAs may be achieved by a recitation of a representative number of DNAs defined by nucleotide sequence or a recitation of structural features common to members of the genus, **which features constitute a substantial portion of the genus**. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed. Applicant is referred to the revised guidelines concerning compliance with the

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written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at [www.uspto.gov](http://www.uspto.gov).

Claims 1-4, 11, 15 and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for gram positive bacteria transformed with a plasmid pFc1 or a Gram-positive thermophilic bacterium transformed with pyruvate decarboxylase gene obtained from *Z. mobilis* or *S.cerevisiae*, of which are known to be heat tolerant and are active at higher temperatures at which thermophiles grow--, does not reasonably provide enablement for such a bacterium transformed with pyruvate decarboxylase isolated from any or all sources including mutants, variants and recombinants. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims 1-4, 11, 15 and 16 are so broad as to encompass any gram positive bacterium transformed with pyruvate decarboxylase isolated from any or all sources. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of pyruvate decarboxylases broadly encompassed by the claims. Since it is well known in the art that thermophilic bacteria grow at an elevated temperature and invariably produce thermo-tolerant enzymes, predictability of which pyruvate decarboxylase available from the innumerable number of sources can be used requires a knowledge of and guidance with regard to which specific ones in the

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large group are tolerant and the detailed knowledge of the isolation, characterization and the CDNA clones of such pyruvate decarboxylase in order to transform any Gram-positive bacterium. Furthermore, since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification in terms of the decarboxylase activity), and detailed knowledge of the ways in which the proteins' structure relates to its function for those skilled in the art contemplating on using variants of pyruvate decarboxylase. However, in this case the disclosure is limited to the Gram-positive bacterium transformed with only two thermotolerant pyruvate decarboxylase obtained either from *Z.mobilis* or *S.cerevisiae*.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass any gram positive bacterium transformed with any *pdh* gene encoding any pyruvate decarboxylase because the specification does **not** establish: (A) regions of the gene structure which may be modified without effecting pyruvate decarboxylase activity; (B) the general tolerance of pyruvate decarboxylase gene to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any pyruvate decarboxylase nucleic acid residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have **not** provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any gram-positive bacteria expressed with any DNA that encode any protein having pyruvate decarboxylase activity. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of pyruvate decarboxylase genes, having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

***CLAIM Rejection - 35 U.S.C 103a***



The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-4, 7-12 and 15-16, are rejected under 35 U.S.C. 103(a) as being unpatentable over Ingram et al. ( WO 95/27064), and Guagliardi et al. (Int. J. Biochem. Cell Biol., 1996, Vol. 284 pp 2239-2246), Payton et al. (FEMS Microbiol let. 1985, 26, pp 333-336) and Martin et al. ( J. Gen. Microbiol, 1993, 139, 1033-1040).

Claims 1-4, 7-12 and 15-16 in this instant application are drawn to a Gram positive bacterium having native alcohol dehydrogenase (adh) activity that has been transformed with a heterologous gene encoding pyruvate decarboxylase (pdc), wherein the bacterium is a *Bacillus sp.*, selected from a group, comprising *B. stearothermophilus*, wherein the heterologous gene is incorporated into the chromosome of the bacterium or the Gram positive bacterium has been transformed with a plasmid comprising the heterologous gene.

Ingram et al. state that *Z. mobilis* and yeast (*S. cerevisiae*) convert carbohydrates ( glucose) to ethanol using *PDC* and *ADH* and to enhance the

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production of ethanol by gram positive bacterium belonging to the *Bacillus sp*, Ingram et al. teach transformed *Bacillus sp* with a plasmid ( also teach chromosomal incorporation) comprising the heterologous pdc and adc .gene from *Z. mobilis* or yeast (*S. cerevisiae*) . However Ingram et al. do not teach a *Bacillus* strain which endogenously produce ADH.

Guagliardi et al. and Payton et al. teach that *B.stearothermophilus*, a Gram-positive *Bacillus* has inherent alcohol dehydrogenase activity. The reference also teaches that the strain can grow at 70<sup>0</sup> C. Martin et al. ( J. Gen. Microbiol, 1993, 139, 1033-1040) teach the advantageous( process at higher temperature, easy to separate ethanol ( via evaporation or distilling), lower cost, low inhibition, etc) use of thermophilic *Bacillus* for ethanol production

In order to enhance the production of ethanol it is obvious for one skilled in the art, to use the thermophilic bacterial strain which has adh activity ( and produce ethanol in "low level") as taught by Guagliardi et al., Payton et al. and Martin et al. and transform it with a plasmid comprising the heterologous gene from *Z. mobilis* or yeast (*S. cerevisiae*) encoding pyruvate decarboxylase ( pdc) as taught by Ingram et al.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mohammad Meah whose telephone number is 571-272-1261. The examiner can normally be reached on 8:30-5PM.


If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

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system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Mohammad Younus Meah, PhD  
Examiner, Art Unit 1652  
Recombinant Enzymes, 3C31 Remsen Bld  
400 Dulany Street, Alexandria, VA 22314  
Telephone: 517-272-1261

  
REBECCA E. PROUTY  
PRIMARY EXAMINER  
GROUP 1652  
1652